Amendments to the Specification:

Please replace the paragraph beginning at page 12, line 2, with the following amended paragraph:

Heregulin 2-α (HRG2-α) is defined herein to be any isolated polypeptide sequence which possesses a biological property of a naturally occurring polypeptide comprising the polypeptide sequence of Fig. 4 (SEQ ID NO:11).

Please replace the paragraph beginning at page 12, line 7, with the following amended paragraph:

"Biological property" for the purposes herein means an *in vivo* effector or antigenic function or activity that is directly or indirectly performed by the Fig. 4 sequence (SEQ ID NO:11) (whether in its native or denatured conformation), or by any subsequence thereof. Effector functions include receptor binding, any enzyme activity or enzyme modulatory activity, any carrier binding activity, any hormonal activity, any activity in promoting or inhibiting adhesion of cells to extracellular matrix or cell surface molecules, or any structural role. However, effector functions do not include possession of an epitope or antigenic site that is capable of cross-reacting with antibodies raised against a polypeptide sequence of Fig. 4 (SEQ ID NO:11). An antigenic function means possession of an epitope or antigenic site that is capable of cross-reacting with antibodies raised against a polypeptide sequence of Fig. 4.

Please replace the paragraph beginning at page 12, line 22, with the following amended paragraph:

Biologically active HRG2-α is defined herein as a polypeptide sharing an effector function of Fig. 4 HRG2-α and which may (but need not) in addition possess an antigenic function. A principal known effect or function of HRG2-α is as a ligand polypeptide having a qualitative biological activity of binding to $p185^{HER2}$ resulting in the activation of the receptor tyrosine kinase. Included within the scope of the HRG2-α as that term is used herein are HRG2-α having translated mature amino acid sequence of the human HRG2-α as set forth in Fig. 4, deglycosylated or unglycosylated derivatives of the HRG2-α, homologous amino acid sequence

variants of the sequence of Fig. 4 (SEQ ID NO:11), and homologous *in vitro*-generated variants and derivatives of the HRG2-α, which are capable of exhibiting a biological activity in common with the HRG2-α of Fig. 4. While native HRG2-α is a membrane-bound polypeptide, soluble forms, such as those forms lacking a functional transmembrane domain, are also included within this definition. In particular, included are polypeptide fragments of the Figure 4 prosequence which have an N-terminal at any residue from about S216 to A227, and its C-terminus at any residue about from K272 to R286, hereinafter the growth factor domain (GFD). For purposes of brevity, reference hereinafter to Figure 4 and HRG2-α shall be read as reference to the GFD fragment.

Please replace the paragraph beginning at page 13, line 12, with the following amended paragraph:

In preferred embodiments, antigenically active HRG2-α is a polypeptide that binds with an affinity of at least about 10^{-9} 1/mole to an antibody raised against the sequence of Fig. 4 (SEQ ID NO:11). Ordinarily the polypeptide binds with an affinity of at least about 10^{-8} 1/mole. Most preferably, the antigenically active HRG2-α is a polypeptide that binds to an antibody raised against the Fig. 4 HRG2-α in its native conformation. Fig. 4 HRG2-α in its native conformation is HRG2-α as found in nature which has not been denatured by chaotropic agents, heat or other treatment that substantially modifies the three dimensional structure of HRG2-α as determined, for example, by migration on nonreducing, nondenaturing sizing gels. Antibody used in this determination is rabbit polyclonal antibody raised by formulating native HRG2-α from a non-rabbit species in Freund's complete adjuvant, subcutaneously injecting the formulation, and boosting the immune response by intraperitoneal injection of the formulation until the titer of anti-HRG2-α antibody plateaus.

Please replace the paragraph beginning at page 13, line 30, with the following amended paragraph:

Ordinarily, biologically or antigenically active HRG2-α will have an amino acid sequence having at least 75% amino acid sequence identity with the translated HRG2-α sequence shown in Fig. 4, more preferably at least 80%, even more preferably at least 90%, and most

preferably at least 95%. Identity or homology with respect to the Fig. 4 sequence is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the residues in Fig. 4, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent homology, and not considering any conservative substitutions as part of the sequence identity. None of N-terminal, C-terminal or internal extensions, deletions, or insertions into the Fig. 4 sequence (SEQ ID NO:11) shall be construed as affecting homology.

Please replace the paragraph beginning at page 14, line 8, with the following amended paragraph:

Thus, the biologically active and antigenically active HRG2-α polypeptides that are the subject of this invention include the sequence of the entire translated nucleotide sequence of Fig. 4 (SEQ ID NO:11); the mature HRG2-α of Fig. 4; fragments thereof having a consecutive sequence of at least 5, 10, 15, 20, 25, 30, or 40 amino acid residues from the Fig. 4 sequence (SEQ ID NO:11); amino acid sequence variants of the Fig. 4 sequence (SEQ ID NO:11) wherein an amino acid residue has been inserted N- or C- terminal to, or within, the Fig. 4 sequence (SEQ ID NO:11) or its fragment as defined above; amino acid sequence variants of the Fig. 4 sequence (SEQ ID NO:11) or its fragment as defined above wherein an amino acid residue of the Fig. 4. sequence (SEQ ID NO:11) or its fragment as defined above wherein an amino acid residue of the Fig. 4 sequence (SEQ ID NO:11) or fragment thereof has been substituted by another residue, including predetermined mutations by, e.g., site-directed or PCR mutagenesis, and other animal species of HRG2-α polypeptides such as rabbit, rat, porcine, non-human primate, equine, murine, and ovine HRG2-α and alleles or other naturally occurring variants of the foregoing and human sequences; derivatives of HRG2-α or its fragments as defined above wherein HRG2-α or its fragments have been covalent modified by substitution, chemical, enzymatic, or other appropriate means, with a moiety other than a naturally occurring amino acid; glycosylation variants of HRG2-α (insertion of a glycosylation site or deletion of any glycosylation site by deletion, insertion or substitution of suitable residues); and soluble forms of the HRG2-α, such as those that lack a functional transmembrane domain. Such fragments and variants exclude any polypeptide heretofore identified, including any known protein or polypeptide of any animal

species fragment, which is otherwise anticipatory under 35 U.S.C. 102 as well as polypeptides obvious over such known protein or polypeptides under 35 U.S.C. 103.

Please replace the paragraph beginning at page 15, line 21, with the following amended paragraph:

Identity or homology with respect to a HRG2-α is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the residues in Fig. 4 (SEQ ID NO:11), after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent homology, and not considering any conservative substitutions as part of the sequence identity. No N- nor C-terminal extensions, deletions nor insertions shall be construed as reducing identity or homology.

Please replace the paragraph beginning at page 16, line 1, with the following amended paragraph:

Preferably, the HRG2-α nucleic acid encodes a polypeptide sharing at least 75% sequence identity, more preferably at least 80%, still more preferably at least 85%, even more preferably at 90%, and most preferably 95%, with the translated amino acid sequence shown in Figure 4 (SEQ ID NO:11). Preferably, the HRG2-α nucleic acid molecule that hybridizes to the nucleic acid sequence of Fig. 4 (SEQ ID NO:10) contains at least 20, more preferably 40, and most preferably 90 bases. Such hybridizing or complementary nucleic acid, however, is further defined as being novel under 35 U.S.C. 102 and unobvious under 35 U.S.C. 103 over any prior art nucleic acid.

Please replace the paragraph beginning at page 16, line 24, with the following amended paragraph:

HRG2-β is defined herein to be any polypeptide sequence which possesses a biological property of a naturally occurring polypeptide comprising the polypeptide sequence of Fig. 8 (SEQ ID NO:7).

Please replace the paragraph beginning at page 19, line 4, with the following amended paragraph:

Thus, the biologically active and antigenically active HRG2-β polypeptides that are the subject of this invention include the sequence of the entire HRG2-β; the HRG2-β fragment of Fig. 8 (SEQ ID NO:7); fragments of HRG2-β having a consecutive sequence of at least 5, 10, 15, 20, or 25 amino acid residues from the HRG2-β sequence amino acids; additional amino acid sequences found in naturally occurring HRG2-β adjacent to the Fig. 8 amino acids (SEQ ID NO:7); amino acid sequence variants of the HRG2-β sequence wherein an amino acid residue has been inserted N- or C-terminal to, or within, the HRG2-β sequence or its fragment as defined above; amino acid sequence variants of the HRG2-β sequence or its fragment as defined above, wherein an amino acid residue of the HRG2-β sequence or fragment thereof has been substituted by another residue, including predetermined mutations by, e.g., site-directed or PCR mutagenesis, and other animal species of HRG2-β–like ligands such as rabbit, rat, porcine, non-human primate, equine, murine, and ovine HRG2-β and alleles or other naturally occurring variants of the foregoing and human sequences; derivatives of HRG2-β or its fragments as defined above wherein HRG2-β or its fragments have been covalent modified by substitution, chemical, enzymatic, or other appropriate means, with a moiety other than a naturally occurring amino acid; glycosylation variants of HRG2-β (insertion of a glycosylation site or deletion of any glycosylation site by deletion, insertion or substitution of suitable residues); and soluble forms of the HRG2-β, such as those that lack a functional transmembrane domain. Such fragments and variants exclude any polypeptide heretofore identified, including any known HRG2-β of any animal species or any known polypeptide fragment which are anticipatory ~~order~~over 35 U.S.C. 102, as well as polypeptides obvious therover under 35 U.S.C. 103.

Please replace the paragraph beginning at page 31, line 8, with the following amended paragraph:

The amino acid sequence of Figure 4 (SEQ ID NO:11) may be proteoloytically processed to create a number of HRG2-α fragments which all contain the amino acid sequence between cysteine 226 and cysteine 265. The amino terminus of the HRG2-α fragment may result from the cleavage of any peptide bond between alanine 1 and cysteine 226, preferably adjacent to

arginine, lysine, valine, or methionine, and most preferably between methionine 45 and serine 46. The carboxy terminus of the HRG2-α fragment may result from the cleavage of any peptide bond between cysteine 265, preferably adjacent to an arginine, lysine, valine, or methionine, and most preferably between lysine 272 and valine 273, between lysine 278 and alanine 279, or between lysine 285 and arginine 286. The resulting HRG2-α ligands resulting from such proteolytic processing are the preferred ligands.

Please replace the paragraph beginning at page 32, line 13, with the following amended paragraph:

There are two principal variables in the construction of amino acid sequence variants: the location of the mutation site and the nature of the mutation. These are variants from the Fig. 4 sequence (SEQ ID NO:11), and may represent naturally occurring alleles (which will not require manipulation of the HRG2-α DNA) or predetermined mutant forms made by mutating the DNA, either to arrive at an allele or a variant not found in nature. In general, the location and nature of the mutation chosen will depend upon the HRG2-α characteristic to be modified. Obviously, such variations that, for example, convert the HRG2-α into a known receptor ligand, are not included within the scope of this invention, nor are any other HRG2-α variants or polypeptide sequences that are not novel and unobvious over the prior art.

Please replace the paragraph beginning at page 83, line 14, with the following amended paragraph:

EGF, AR, HB-EGF and TGF-α are all newly synthesized as membrane anchored proteins by virtue of their transmembrane domains. The proproteins are subsequently processed to yield mature active molecules. In the case of TGF-α there is evidence that the membrane associated proforms of the molecules are also biologically active (Brachmann, R., *et al.* (1989) Cell 56: 691-700), a trait that may also be the case for HRG2-α. EGF is synthesized as a 1168 amino acid transmembrane bound proEGF that is cleaved on the amino-terminal end between arginine 970 and asparagine 971 and at the carboxy-terminal end between arginine 1023 and histidine 1024 (Carpenter, G., and Cohen, S. (1979) Ann. Rev. Biochem. 48: 193-216), to yield the 53 amino acid mature EGF molecule containing the three loop, 3 disulfide bond signature structure.

The 252 amino acid proAR is cleaved between aspartic acid 100 and serine 101 and between lysine 184 and serine 185 to yield an 84 amino acid form of mature AR and a 78 amino acid form is generated by NH_2-terminal cleavage between glutamine 106 and valine 107 (Plowman, G.D. *et al.,* (1990) Mol. Cell. Biol. 10: 1969-1981). HB-EGF is processed from its 208 amino acid primary translation product to its proposed 84 amino acid form by cleavage between arginine 73 and valine 74 and a second site approximately 84 amino acids away in the carboxy-terminal direction (Higashiyama, S., *et al.,* and Klagsburn, M. (1991) Science 251: 936-939). The 160 amino acid preproform of TGF α is processed to a mature 50 amino acid protein by cleavages between alanine 39 and valine 40 on one side and downstream cleavage between alanine 89 and valine 90 (Derynck *et al.,* (1984) Cell: 38: 287-297). For each of the above described molecules COOH-terminal processing occurs in the area bounded by the sixth cysteine of the EGF motif and the beginning of the transmembrane domain. The COOH-terminal processing site of mature HRG2-α has not been defined, however several sites seem plausible candidates ie, lysine 272-valine 273, lysine 278-alanine 279, or lysine 285-arginine 286 (fig 4). The NH2-terminal end of HRG2-α likewise has not been determined; preliminary amino acid sequence analysis of the mature molecule indicates that processing may occur between methionine 45 and serine 46 or further on toward the NH2-terminus.

Please replace the paragraph beginning at page 84, line 30, with the following amended paragraph:

The isolation of full-length cDNA of HRG2-α is accomplished by employing the DNA sequence of Fig 4 (SEQ ID NO:10) to select additional cDNA sequences from the cDNA library constructed from human MDS-MB-321. Full-length cDNA clones encoding HRG2-α are obtained by identifying cDNAs encoding HRG2-α longer in both the 3' and 5' directions and then splicing together a composite of the different cDNAs. Additional cDNA libraries are constructed as required for this purpose. Following are three types of cDNA libraries that may be constructed: 1) Oligo-dT primed where predominately stretches of polyadenosine residues are primed, 2) random primed using short synthetic deoxyoligonucleotides non-specific for any particular region of the mRNA, and 3) specifically primed using short synthetic

deoxyoligonucleotides specific for a desired region of the mRNA. Methods for the isolation of such cDNA libraries was previously described.